REMARKS

Applicants submit concurrently herein a substitute specification in a clean and marked up version. The substitute specification is amended to recite the appropriate section headings.

Applicants have amended claim 1 incorporating the features of claim 8. As amended claim 1 recites "...and a pharmaceutically compatible inert carrier or diluent." Support for this amendment is found, e.g., on page 8, 2nd paragraph of the specification.

Applicants have cancelled claim 8 without prejudice.

Applicants have amended claim 4 to recite "Bis(O-isopropyl-dithiocarbonato)palladium(II)" rather than "Bis-isopropyl-dithiocarbonato) palladium(II)" and have amended claim 10 to recite "parvocellular. . ." rather than "the parvocellular."

Applicants have also amended claim 11 to recite:

> 11. A method for the treatment of ~~a cancerous disease~~ an autoimmune disease comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical preparation according to claim 1.

Support for this amendment is found in original claim 11 which recited a "Use" claim for the treatment of an autoimmune disease rather than a cancerous disease and on page 1, last paragraph and page 7, line 22 to page 9, line 3 of the application as initially filed.

Claims 9, 10 and 12 stand rejected under 35 U.S.C. 112, second paragraph, for purportedly being incomplete. In particular the Examiner contends that the claims omit essential steps. Applicants have amended claims

9 and 12 to more clearly describe the claimed invention. As amended the claims recite:

> 9. A method for the treatment of cancerous disease comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical preparation according to claim 1.
>
> 12. A process for the production of a pharmaceutical preparation according to claim 1, comprising mixing the compound according to formula (I) with a pharmaceutically compatible carrier or diluent.

Support for these amendments is found e.g. on page 2, lines 1-7, and page 7, line 22 to page 9, line 3 in the application as initially filed.

In view of the foregoing remarks and amendments to the claims, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 9, 10 and 12 under 35 U.S.C. 112, second paragraph.

Claims 1-4 and 7 stand rejected under 35 U.S.C. 102(b) for purportedly being anticipated by Watt et al. (J. Inorganic Nuclear Chemistry 1965) ("Watt et al."). Applicants respectfully disagree.

> Anticipation under 35 U.S.C. §102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention.
>
> *Electro Med. Sys. S.A. v. Cooper Life Sciences*, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

Applicants have amended claim 1 such that the claimed pharmaceutical preparation additionally includes "...a pharmaceutically compatible inert carrier or diluent". Watt et al. do not disclose pharmaceutical preparations and thus do not teach each and every limitation of the claimed invention. Therefore, Watt et al. do not anticipate claims 1-4 or 7.

In view of the foregoing remarks and amendments to the claims, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-4 and 7 under 35 U.S.C. 102(b) in view of Watt et al.

Claims 1-12 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Watt et al. in view of Amtmann et al. (US 2002/0004526)("Amtmann et al."). Applicants respectfully disagree.

The claimed pharmaceutical Pd-preparations show a seven to ten times higher effectiveness compared to the Pt-complexes disclosed in Amtmann et al. (c.f. present specification, page 6, 2nd paragraph, line 15; Table 1). It is shown in Table 1 on page 13 that Bis(O-isopropyl-dithiocarbonato)palladium (II) (subst.-number 2) has IC_{50}-values at pH 6.8 of 0.6 and 0.8, respectively, while the value of the corresponding platinum compound of Amtmann et al. is 6. Despite the increased effectiveness, the toxicity of the claimed pharmaceutical preparations is low and, thus, it is possible to achieve the maximum tolerable dose without any problems. On the other hand, the maximum tolerable and maximum therapeutic dosage of the platinum compounds according to Amtmann et al. cannot be achieved due to their poor solubility, thereby not achieving the full therapeutic potential of the compounds (page 1, 3rd paragraph of the specification).

Hence, Applicants have demonstrated superior results of the claimed preparations, which overcome the drawbacks of the Pt-compounds according to Amtmann et al. due to their poor solubility, because the pharmaceutical preparations according to the present invention have an unexpected, significantly higher anti-tumor activity. *In re Wiechert*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967)

A person skilled in the art could not derive or expect this from the combined teachings of Amtmann et al. and Watt et al.

Amtmann et al. do not suggest or motivate a skilled person to replace the platinum with any other metal, in particular with palladium. Amtmann et al. relates to platinum anti-tumor agents and describe platinum-xanthogenate complexes as alternatives to the well known platinum containing drug Cisplatin. Hence, Amtmann et al. do not contain any incentive to use a non-platinum metal agent.

Watt et al. do not overcome the deficiencies of Amtmann et al., because Watt et al. do not teach or suggest any therapeutic utility of xanthogenate complexes. Watt et al. disclose platinum, palladium, nickel, chromium and cobalt complexes. No expectation of any advantage can be derived from Watt et al., if platinum is replaced by any one of palladium, nickel, chromium or cobalt. Therefore, a person skilled in the art would not have been motivated to select palladium for making the pharmaceutical preparations of the invention.

It is evident that the kind of the central metal plays a critical role in the activity of the complexes. The enclosed reference of Friebolin et al. (J. Med. Chem. 2005, 48, 7925-7931) examines the structure-activity relationships among metal-xanthate complexes. The cytotoxic activity on tumor cells of xanthate complexes of platinum, palladium, gold, nickel, copper, rhodium and bismuth were compared with each other. Among those, the claimed palladium complexes showed the most pronounced anti-tumor effect (see Figure 1, compound numbers 4-6). On the other hand, nickel complexes (compound numbers 8-10) having exactly the same planar structure as the palladium and platinum complexes (see Figure 3) showed a substantially weaker activity than the palladium as well as the platinum complexes (compound numbers 2-6). Thus, it is evidenced by the later published reference of Friebolin et al. that it was unpredictable based on the structural similarities of the metal complexes which transition metal may cause a better effectiveness of the xanthate complexes at the time the application was filed. Therefore, it was not obvious to select palladium to make complexes

superior to that of platinum. Thus, the combination of Watt et al. and Amtmann et al. fails to render claim 1-12 obvious.

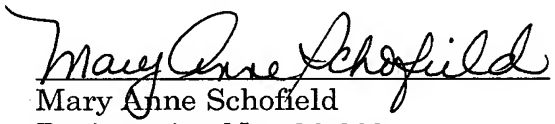
In view of the foregoing remarks and amendments to the claims, Applicants respectfully request that the Examiner reconsider the rejection of claim 1-12 under 35 U.S.C. 103(a) in view of Watt et al. in combination with Amtmann et al.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #99380.B270041).

Respectfully submitted,

February 21, 2008



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Articles

Antitumoral Activity of Non-Platinum Xanthate Complexes

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To establish structure–activity relationships, derivatives of bis(*O*-alkyldithiocarbonato)-platinum(II) complexes were analyzed. Eighteen bis(*O*-alkyldithiocarbonato) metal complexes were synthesized, and their cytotoxic activity on two human cancer cell lines was compared with the corresponding platinum bis(*O*-alkyldithiocarbonato) complexes and cisplatin. Complexes were synthesized with palladium, gold, nickel, copper, rhodium, and bismuth. Palladium and bismuth complexes were found to display significant cytotoxic activity. Palladium complexes were most active with up to 10-fold lower IC_{50} values as compared with the corresponding platinum complexes. The other complexes were only poorly active. Palladium, bismuth, and nickel complexes were more active at pH 6.8 than at pH 7.4. This difference in activity was most pronounced with palladium complexes. A pH of 6.8 and lower has been frequently found in solid tumors. Drugs with such pH dependent activity are supposed to have an improved therapeutic index as compared to drugs that are active irrespective of pH.

Introduction

Chemotherapy is one of the major therapeutic tools in cancer treatment. Despite severe side effects, cisplatin is one of the most frequently used anticancer drugs. Since the introduction of cisplatin thousands of platinum complexes have been synthesized and tested for antitumoral activity. Some compounds such as Carboplatin, oxaliplatin, and nedaplatin showing improved activity or reduced toxicity were identified and are now in clinical use.[1,2] All platinum complexes in clinical use have some common structural features. They contain two easily removable ligands in a cis-position and two strongly bound amino ligands.

The success as well as the limitations of cisplatin prompted investigation of other metals. Antitumoral complexes with yttrium (Y), titanium (Ti), vanadium (V), molybdenum (Mo), technetium (Tc), rhenium (Re), iron (Fe), ruthenium (Ru), osmium (Os), cobalt (Co), rhodium (Rh), iridium (Ir), nickel (Ni), palladium (Pd), copper (Cu), gold (Au), and bismuth (Bi) were described.[3–6] Again, the active complexes were of the diammino type.

Until now, only four non-platinum metal antitumor agents have entered early clinical trials. Gallium trinitrate and spirogermanium have already passed phase II clinical studies and have shown limited cytostatic activity against certain human carcinomas and lymphomas.[7] The two early transition metal complexes budotitane and titanocene dichloride have just reached the end of phase I clinical trials and have been found to have an unusual pattern of organ toxicity in man.[8]

Recently platinum complexes with antitumoral activity using sulfur as complex forming atoms were described.[9,10] These complexes are between 2- and 3-fold more cytotoxic under slightly acidic conditions (pH 6.8) as compared to pH 7.4. This effect is remarkable, as in solid tumors slightly acidic conditions were frequently observed. Due to anaerobic fermentation, glucose is converted to lactic acid, which is secreted from tumor cells.[11] As a consequence the pH drops to values between pH 6.8 and 6.5. Therefore, drugs with cytotoxicity depending on low pH appear to be endowed with a favorable therapeutic index.[12,13] Indeed, thioplatin was found to display antitumoral activity in human cancer xenocrafts in nude mice at nontoxic doses.

In a recent publication we have described the antitumoral effects of derivatives of thioplatin. The lipophilic ethyl residues of thioplatin were altered, while the central xanthate structure remained unchanged. New derivatives with significantly higher antitumoral activity could be identified.[10]

Here we describe the toxic effects of new non-platinum xanthate complexes on tumor cells. Xanthate residues which were highly effective in platinum complexes were used to synthesize bismuth, copper, gold, nickel, palladium, and rhodium complexes.

Results and Discussion

Cytotoxic Activity at pH 6.8. We recently tested several platinum xanthate complexes for antitumoral activity and could demonstrate that complexes of secondary xanthates are more active than complexes of primary xanthates with the same number of C-atoms. Complexes of large lipophilic xanthates were significantly less active. While the ethylxanthate complex was endowed with intermediate antitumoral potential, the

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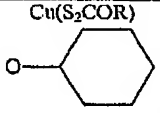
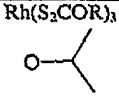
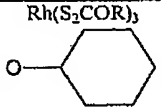
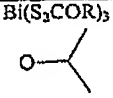
Table 1. (Continued)

Compound number	structure	IC_{50} Calu-6			IC_{50} MCF7		
		pH 6.8	pH 7.4	pH 7.4/ pH 6.8	pH 6.8	pH 7.4	pH 7.4/pH 6.8
	$Cu(S_2COR)$ 	ND	ND	ND	ND	ND	ND
12	$Rh(S_2COR)_3$ 	289.60	289.60	1.00	289.60	289.60	1.00
13	$Rh(S_2COR)_3$ 	180.83	194.06	1.07	179.04	204.09	1.14
14	$Bi(S_2COR)_3$ 	13.85	16.86	1.22	21.05	24.66	1.17
15	$Bi(S_2COR)_3$ 	11.06	11.20	1.01	14.10	19.34	1.37
16	$Bi(S_2COR)_3$ 	16.76	16.33	0.97	120.42	109.37	0.91

[a] Human cancer cell lines were treated with various concentrations of each complex. IC_{50} values were determined from dose−response curves. ND: not determined due to lack of solubility.

isopropyl- and cyclohexylxanthate complexes were found to display the highest cytotoxic potential.[10] In order to study the function of the central metal in the antitumoral activity of thioplatins, we decided to synthesize the ethyl-, isopropyl-, and cyclohexylxanthate complexes of bismuth, copper, gold, nickel, palladium, and ruthenium. All derivatives except the Rh ethylxanthate complex, which was unstable, could be synthesized. The Cu isopropyl and cyclohexyl and the Au ethyl and isopropyl derivatives were insoluble in all biologically compatible solvents. Therefore, we were unable to analyze these complexes in our tumor cell models.

The antitumoral potential of the complexes was evaluated in two human cancer cell lines which were either highly (Calu-6) or poorly (MCF-7) sensitive to cisplatin.[14,15] The effect on the mammary cancer line MCF-7 was of specific interest, as mammary cancer is refractory to treatment with all platinum complexes currently in clinical use. It is a remarkable feature of platinum xanthate complexes that MCF-7 cells are highly sensitive while they survive significantly higher doses of cisplatin.

The cytotoxic activity of the new complexes was studied, both at pH 6.8 which is found in solid tumors and at pH 7.4, which was found in normal tissue. Dose−response curves were established for each compound, and the concentration which is sufficient to reduce the cell number by 50% (IC_{50}) was calculated. The IC_{50} at pH 6.8, which we believe is likely to be the condition relevant for clinical application, was used for quantitative assessment of the antitumoral potential of each compound. The IC_{50} values are enlisted in Table 1 (see also Figure 1).

Palladium. The palladium complexes (**4**−**6**) were identified as the most active derivatives. IC_{50} values varied between 0.1 and 0.47 μM in Calu-6 and between 0.45 and 1.17 μM in MCF-7 cells. The lowest IC_{50} value was obtained with the isopropyl derivative (**5**) in both cell lines. 260- and 272-fold lower IC_{50} values when compared with cisplatin were found in Calu-6 (0.1 μM/26.04 μM) and in MCF-7 cells (0.45 μM/122.5 μM), respectively. The isopropyl derivative (**5**) was 4.7- and 3.2-fold more active in Calu-6 cells than the cyclohexyl derivative (**6**) and the ethyl derivative (**4**). In MCF-7 cells this was also the most active derivative (**5**).

Gold. The cyclohexyl gold derivative (**7**) displayed some activity. Similar IC_{50} values were found in Calu-6 (52.81 μM) and MCF-7 cells (71.55 μM).

Nickel. All nickel derivatives displayed intermediate activity in both cell lines (**8**−**10**). In Calu-6 cells IC_{50} values varied between 52.47 and 76.72 μM, in MCF-7 cells between 66.29 and 95.1 μM. There was no significant difference in the activity of the individual compounds on Calu-6 and MCF-7.

Copper. The copper ethyl derivative had only low activity. IC_{50} values of 144.24 and 113.75 μM were found (**11**).

Rhodium. The rhodium compounds were found to have the lowest cytotoxic activity of all derivatives tested in this study (**12**, **13**). The isopropyl derivative

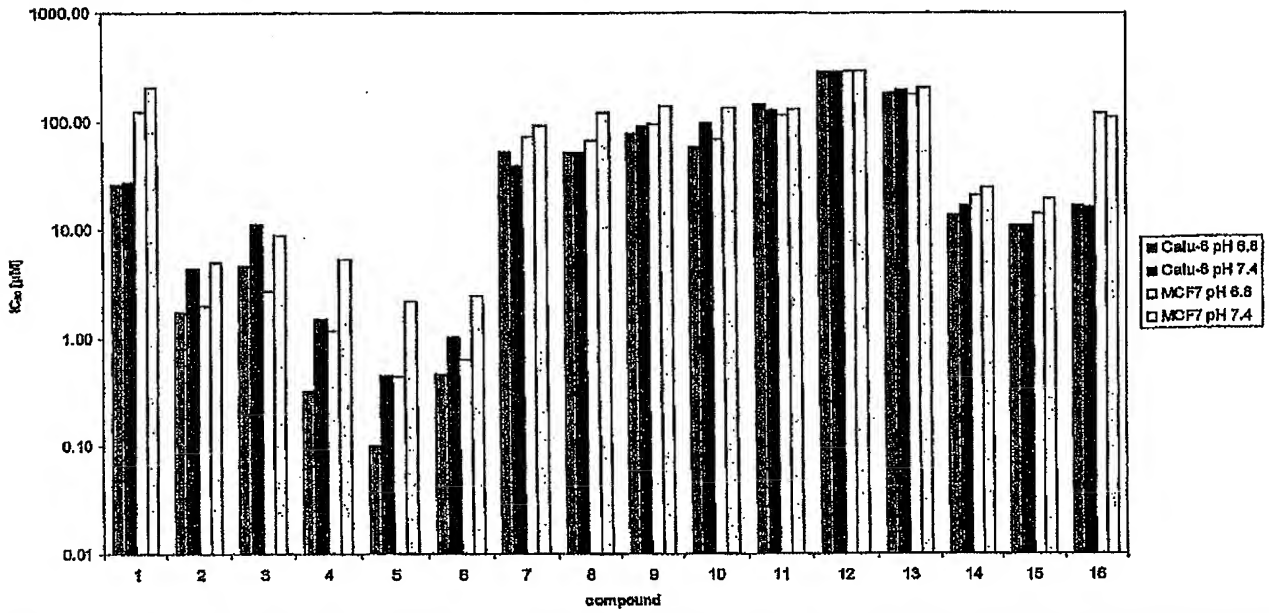


Figure 1. Antitumoral activity of metal xanthate complexes. Data from Table 1 are displayed. IC_{50} values were calculated from dose–response curves. Blue: Calu-6 cells treated at pH 6.8. Violet: Calu-6 cells treated at pH 7.4. Yellow: MCF-7 cells treated at pH 6.8. Green: MCF-7 cells treated at pH 7.4.

was not toxic for both tumor lines even at the highest concentration that could be applied (100 μg/mL) (**12**). The cyclohexyl derivative was marginally active (**13**). For Calu-6 and MCF-7 cells IC_{50} values of 180.83 μM and 179.04 μM were obtained at pH 6.8, respectively.

Bismuth. All bismuth derivatives (**14**–**16**) displayed cytotoxic activity (**14**–**16**). The sensitivity of Calu-6 cells was in a similar range for all derivatives. IC_{50} values of 11.06, 13.85, and16.76 μM were obtained. The ethyl and the isopropyl derivative were toxic to MCF-7 cells in the same dose level, with IC_{50} values of 21.05 and 14.1 μM (**14** and **15**). In contrast, the cyclohexyl derivative (**16**) was significantly less active in MCF-7 (**16**). The concentration had to be elevated to 120.4 μM in order to obtain the IC_{50}.

Effect of pH. Due to production of lactic acid a slightly acidic milieu of pH 6.8 is frequently encountered in solid tumors, as compared to pH 7.2–7.4 in normal tissues. It is one of the advantageous features of platinum xanthates that they are more toxic at pH 6.8 as compared to pH 7.4. It was, therefore, of importance to study the differential activity of the non-platinum xanthate complexes at pH 6.8 and pH 7.4. In order to get an overview of the central metal function in the pH effect of platinum xanthates we calculated the $pH_{7.4/6.8}$ quotient (IC_{50} at pH 7.4/IC_{50} at pH 6.8) for each derivative in both cell lines. Mean values of the $pH_{7.4/6.8}$ quotients were calculated for both cell lines and for all complexes with each metal. The results are shown in Figure 2. Surprisingly, only platinum, palladium, and to a much lesser extent nickel complexes were significantly more active at pH 6.8. In the case of cisplatin and the xanthate complexes of gold, copper, rhodium, and bismuth, $pH_{7.4/6.8}$ quotients did not differ significantly from 1. For platinum and for palladium, $pH_{7.4/6.8}$ quotients of 2.69 ± 0.39 and 4.10 ± 0.99 were found, respectively. Palladium complexes displayed a statistically significant higher $pH_{7.4/6.8}$ quotient than platinum

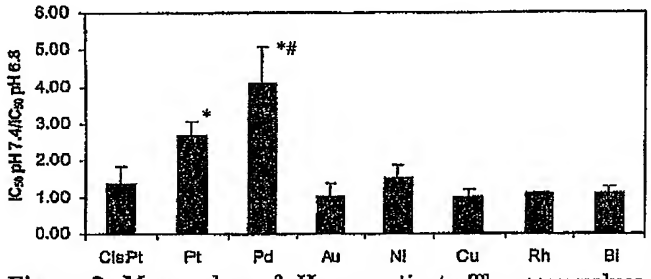


Figure 2. Mean values of $pH_{7.4/6.8}$ quotients. The mean values of the $pH_{7.4/6.8}$ quotients were calculated for all results obtained with each given metal on Calu-6 and MCF-7 cells. (*) Difference to cisplatin significant at $P < 0.01$. (#) Difference to platinum xanthate complexes significant at $P < 0.01$.

xanthate complexes with (P value 0.015, Student's t-test), and the difference to cisplatin ($pH_{7.4/6.8}$ quotient 1.37 ± 0.47) was statistically significant for both $pH_{7.4/6.8}$ quotients ($P < 0.01$). The $pH_{7.4/6.8}$ quotient of nickel, 1.51 ± 0.36, is of low biological significance, although the effect is statistically significant ($P < 0.009$).

In a previous publication we analyzed the structure–activity relationship of platinum xanthate complexes.[10] In that panel of compounds, we found the $pH_{7.4/6.8}$ quotients to vary between 1.4 and 2.8. It can be concluded that the structure of the xanthate residue has some influence on the $pH_{7.4/6.8}$ quotient. In this study, we find $pH_{7.4/6.8}$ quotients between 1.0 (Cu) and 4.1 (Pd). It is evident that the central metal plays an essential role in the pH dependent activity of antitumoral xanthate complexes. So far we can only speculate about the underlying chemical mechanism. First of all, it is remarkable that all three pH sensitive complexes have the same planar structure (Figure 3). The other complexes have different structures (Figure 3) and display similar cytotoxic activity at pH 6.8 and pH 7.4. The quantitative differences between Ni, Pt, and Pd may be

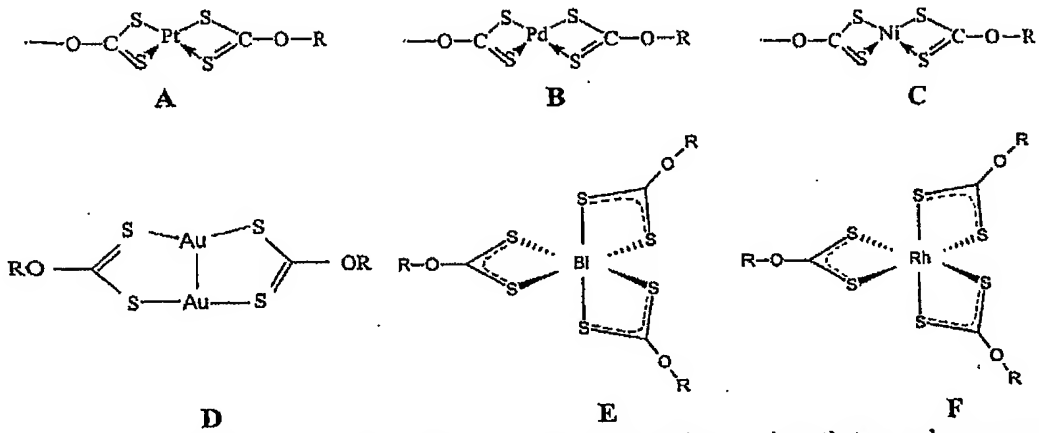


Figure 3. Structures of metal xanthate complexes. Structures of representative metal xanthate complexes were determined by X-ray diffraction analysis. (A) Platinum. (B) Palladium. (C) Nickel. (D) Gold. (E) Bismuth. (F) Rhodium.

either the result of different reactivity of these metals to cellular targets or due to a different tightness of the xanthate/metal complex. Further detailed chemical studies are necessary to address this phenomenon.

The facts that palladium complexes are approximately 10-fold more active than the corresponding platinum complexes and that they display significantly improved $pH_{7.4/6.8}$ quotients make these complexes promising candidates for a more detailed analysis of their antitumoral potential. Cytotoxicity is only one aspect of an antitumor drug. The in vivo toxocity and efficacy of the different complexes will be the next important features to be evaluated.

Experimental Section

Cell Lines. Calu-6 (adenocarcinoma, lung) and MCF 7 (mamma carcinoma) were obtained from ATCC and were cultivated according to the instructions of the supplier at 37 °C, 5% CO_2, and 100% relative humidity.

Control of pH. In order to obtain cultivation conditions at pH 6.8, media containing 0.85 g of $NaHCO_3$/L were prepared. To each 50 mL of fetal calf serum, 1 mL of 1 N HCl was added to neutralize $NaHCO_3$ present in serum. After incubation for 30 min in 5% CO_2 a pH of 6.8 was obtained in the cultures. This pH was stable for at least 12 h with all cell lines used.

A pH of 7.4 was obtained with medium containing 2.2 g of $NaHCO_3$/L.

Cytotoxicity Assay. For in vitro experiments stock solutions of the metal complexes in acetone were prepared (1 mg/mL).

Acetone was applied in tissue culture up to a concentration of 5%. At this concentration cellular growth rates remained unaffected (data not shown). A maximum concentration of 50 μg/mL was obtained for compounds with a solubility of at least 1 mg/mL. For compounds with lower solubility the corresponding maximum dose was accordingly lower.

Cells were plated in 96-well plates at a density of 2×10^6 cells/plate. One day later culture medium was replaced by medium of the desired pH. After equilibration to an atmosphere containing 5% CO_2, test compounds were added in quadruplicate. Serial 1:2 dilutions were prepared directly in the plates using multichannel pipets. The resulting concentrations were 100, 50, 25, 12.5, 6.25, 3.1, 1.6 μg/mL. In the case of highly active palladium compounds serial dilutions covered the range between 2.5 and 0.04 μg/mL. After 2 h incubation at 37 °C the culture medium was discharged and replaced with 100 μL of fresh inhibitor free medium of pH 7.4. Cell cultures were incubated until untreated controls had grown confluent (between 24 and 96 h, depending on growth rate). Cells were fixed with 3% formaldehyde solution and stained with 1% crystal violet. The amount of bound crystal violet which is linear with adherent living cells was determined in an Antos 2001 ELISA reader at a wavelength of 550 nm. In the cases of MCF 7, which do not form a homogeneous cell layer, the dye was eluted with 200 μL of ethanol/1% acetic acid before OD 550 nm was determined. The IC_{50} values were taken from dose–response curves.

Chemistry. Instrumentation. Melting points were determined in open capillaries with a Büchi electrothermal melting point apparatus and are not corrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brucker AC 300 instrument operating at 300 and 75 MHz, respectively. Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as an internal reference. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), c (centered). Infrared spectra were recorded on a Brucker Vector 22 in KBr. The following abbreviations are used to describe the peak intensity: w (weak), m (medium), s (strong). UV spectra were recorded on a Hewlett-Packard HP 8452 A spectrophotometer in CH_2Cl_2 as solvent. The absorption maxima λ_{max} are reported in nm, the extinction coefficient ϵ in $dm^{-3}\ mol^{-1}\ cm^{-1}$. Mass spectra were obtained with a JEOL JMS-700 (FAB, positive mode, matrix was *m*-nitrobenzyl alcohol). Combustion analysis (C, H, S) was performed on an Elementar vario EL and the results were within ±0.4% of the theoretical values. All commercially available chemicals were used as received (solvents in p.a. quality).

Xanthates. All alkylxanthates were prepared according to previously published procedures.[16,17] Xanthates were purified by crystallization or precipitation from acetone–diethyl ether or pentane. Colorless to bright yellow crystals or solids were obtained.

Palladium Compounds. All of the Pd compounds used in this study (4–6) were described previously.[17–20]

Bis(*O*-alkyl-dithiocarbonato)palladium(II) complexes were synthesized by reaction of the corresponding potassium *O*-alkyl-dithiocarbonates (KS_2COR) with dipotassium tetrachloropalladate(II) (K_2PdCl_4) by the following general procedure.[17,20]

K_2PdCl_4 (1.53 mmol) dissolved in 5 mL of distilled H_2O and 4.60 mmol of the potassium *O*-alkyl-dithiocarbonate (KS_2COR) dissolved in 5 mL of distilled H_2O were added quickly and, with vigorous stirring, an additional 5 mL of distilled H_2O was added. Instant precipitation of the product was observed. The reaction vessel was closed, and the mixture was stirred for 80–120 min at room temperature. The precipitate was collected by suction filtration and washed three times with distilled H_2O followed by washings in diethyl ether or pentane. Crystallization from acetone or acetone/$CHCl_3$ yielded the Pd complexes as yellow or brown crystals. To remove solvent residues the crystals were dried in vacuo for 1–2 days.

For $Pd(S_2COiPr)_2$ (5) and $Pd(S_2COcHex)_2$ (6) the structure of each complex was determined by X-ray diffraction analysis. A planar structure comparable to that of $Pd(S_2COCH_2CH_3)_2$[21] and platinum xanthates was found.

All Pd−xanthate complexes were found to be insoluble in water, slightly soluble in acetone, and soluble in $CHCl_3$ (4−6).

Bis(*O*-ethyl-dithiocarbonato)palladium(II) (4): $Pd(S_2COEt)_2$, yield 79% (brown-gold crystals); mp 152 °C (acetone).

Bis(*O*-isopropyl-dithiocarbonato)palladium(II) (5): $Pd(S_2COiPr)_2$, yield 79% (orange crystals); mp 143 °C (acetone).

Bis(*O*-cyclohexyl-dithiocarbonato)palladium(II) (6): $Pd(S_2COcHex)_2$, yield 82% (brown crystals); mp 165 °C (dec; acetone/$CHCl_3$).

Gold Compounds. Some gold(I) xanthate derivatives were described previously.[22] Gold cyclohexylxanthate has not been previously published. All (*O*-alkyl-dithiocarbonato)gold(I) complexes were synthesized by reaction of the corresponding potassium *O*-alkyl-dithiocarbonates (KS_2COR) with potassium tetrachloroaurate(III) ($KAuCl_4$) by the following general procedure.[22]

Potassium *O*-alkyl-dithiocarbonate (3.97 mmol; KS_2COR) was dissolved in 4 mL of distilled H_2O. $KAuCl_4$ (0.87 mmol) dissolved in 3 mL of distilled H_2O was added quickly and with vigorous stirring. The reaction vessel was closed, and the mixture was stirred for 1−3 h at room temperature. The precipitate was collected by suction filtration and washed three times with distilled H_2O followed by diethyl ether. The product was crystallized from $CHCl_3$. To remove solvent residues the crystals were dried in vacuo for 1−2 days.

The structures of all (*O*-alkyl-dithiocarbonato)gold(I) complexes were verified by IR spectroscopy, elemental analysis, NMR, and mass spectrometry. In the case of $Au(S_2COiPr)$ X-ray diffraction was possible. It turned out that $Au(S_2COiPr)$ is better described by the dimeric form $[Au_2(S_2COiPr)]$. This result is in accordance with the recently published structure of $Au_2(S_2COnBu)_2$.[23]

(*O*-Cyclohexyl-dithiocarbonato)gold(I) (7): $Au_2(S_2COcHex)_2$, yield 99% (orange solid); mp 160 °C (dec; $CHCl_3$).

(*O*-Isopropyl-dithiocarbonato)gold(I): $Au(S_2COiPr)_2$, yield 96% (orange solid); mp 135 °C (dec; $CHCl_3$).

Nickel Compounds. All bis(*O*-alkyl-dithiocarbonato)nickel(II) complexes used in this study were described previously.[24] The compounds were synthesized by reaction of the corresponding potassium *O*-alkyl-dithiocarbonates (KS_2COR) with nickel dichloride hexahydrate ($NiCl_2 \cdot 6H_2O$) by the following general procedure.

Potassium *O*-alkyl-dithiocarbonate (6.3 mmol, KS_2COR) was dissolved in 10 mL of distilled H_2O, and 2.1 mmol of $NiCl_2 \cdot 6H_2O$ dissolved in 5−10 mL of distilled H_2O was added quickly and with vigorous stirring. The reaction vessel was closed and the mixture stirred for 30−60 min at room temperature. The precipitate was collected by suction filtration and washed three times with distilled H_2O and pentane. The product was crystallized from acetone or diethyl ether/pentane. To remove solvent residues the crystals were dried in vacuo for 1−2 days.

Bis(*O*-ethyl-dithiocarbonato)nickel (II) (8): $Ni(S_2COEt)_2$, yield 83% (black crystals); mp 135 °C (acetone).

Bis(*O*-isopropyl-dithiocarbonato)nickel(II) (9): $Ni(S_2COiPr)_2$, yield 81% (black crystals); mp 114 °C (diethyl ether/pentane).

Bis(*O*-cyclohexyl-dithiocarbonato)nickel(II) (10): $Ni(S_2COcHex)_2$, yield 47% (dark green crystals); mp 168 °C (dec; diethyl ether/pentane).

Copper Compound. Potassium *O*-ethyl-dithiocarbonate (20 mmol, KS_2COEt) was dissolved in 8 mL of distilled H_2O, and 2.00 mmol of $CuSO_4 \cdot 5H_2O$ dissolved in 5 mL of distilled H_2O was added quickly and with vigorous stirring. A brown colored solid precipitate which changed its color slowly to yellow was obtained. The reaction vessel was closed and the mixture further stirred for 45 min at room temperature. The precipitate was collected by suction filtration and washed three times with distilled H_2O and then with diethyl ether. To remove solvent residues the solid was dried in vacuo for 1 day.

Due to the insolubility of Cu xanthates only an IR spectrum and the combustion analysis could be recorded.

(*O*-Ethyl-dithiocarbonato)copper(I) (11): $Cu(S_2COEt)$, yield 96% (yellow solid); mp 165 °C (dec).

Rhodium Compounds. All tris(*O*-alkyl-dithiocarbonato)-rhodium(III) complexes were synthesized by reaction of the corresponding potassium *O*-alkyl-dithiocarbonates (KS_2COR) with trisodium hexachlororhodate(III) (Na_3RhCl_6) by the following general procedure.[25,26]

Na_3RhCl_6 (0.26 mmol) was dissolved in 2 mL of distilled H_2O, and 1.04 mmol of the potassium *O*-alkyl-dithiocarbonate (KS_2COR) dissolved in 3 mL of distilled H_2O was added quickly with vigorous stirring. Slowly a yellow solid precipitated. The reaction vessel was closed, and the mixture was stirred for 3−4 h at room temperature. The precipitate was collected by suction filtration and washed three times with distilled H_2O and then with pentane. The product was crystallized from acetone/$CHCl_3$ or diethyl ether/pentane. To remove solvent residues the crystals were dried in vacuo for 1−2 days.

Tris(*O*-isopropyl-dithiocarbonato)rhodium(III) (12): $Rh(S_2COiPr)_3$, yield 47% (yellow-orange crystals); mp 175 °C (dec; diethyl ether/pentane).

Tris(*O*-cyclohexyl-dithiocarbonato)rhodium(III) (13): $Rh(S_2COcHex)_3$, yield 51% (yellow-brown crystals); mp 152 °C (acetone/$CHCl_3$).

Bismuth Compounds. All three tris(*O*-alkyl-dithiocarbonato)bismuth(III) complexes were described previously[27−30] and were synthesized by reaction of the corresponding potassium *O*-alkyl-dithiocarbonates (KS_2COR) with bismuth trichloride ($BiCl_3$) by the following general procedure.[28−30]

$BiCl_3$ (1.59 mmol) was dissolved in 10 mL of ethanol, and 4.76 mmol of the potassium *O*-alkyl-dithiocarbonate (KS_2COR) dissolved in 10 mL of 80% ethanol/ 20% water was added quickly and with vigorous stirring. The reaction vessel was closed, and the mixture was stirred for 10−60 min at room temperature. The yellow precipitate was collected by suction filtration and washed three times with distilled H_2O, once with ethanol, and once with pentane. The product was crystallized from $CHCl_3$/pentane. To remove solvent residues the crystals were dried in vacuo for 1−2 days.

Tris(*O*-ethyl-dithiocarbonato)bismuth(III) (14): $Bi(S_2COEt)_3$, yield 77% (yellow crystals); mp 103 °C ($CHCl_3$/pentane).

Tris(*O*-isopropyl-dithiocarbonato)bismuth(III) (15): $Bi(S_2COiPr)_3$, yield 72% (yellow crystals); mp 136°C (dec; $CHCl_3$/pentane).

Tris(*O*-cyclohexyl-dithiocarbonato)bismuth(III) (16): $Bi(S_2COcHex)_3$, yield 81% (yellow crystals); mp 138°C (dec; $CHCl_3$/pentane).

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Supporting Information Available: Spectroscopic data and elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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